# SHANK3 and IGF1 restore synaptic deficits in neurons from 22q13 deletion syndrome patients.

**Journal:** Nature

**Publication Year:** 2013

**Authors:** Aleksandr Shcheglovitov, Olesya Shcheglovitova, Masayuki Yazawa, Thomas Portmann, Rui Shu, Vittorio Sebastiano, Anna Krawisz, Wendy Froehlich, Jonathan A Bernstein, Joachim F Hallmayer, Ricardo E Dolmetsch

**PubMed link:** 24132240

**Funding Grants:** Stanford CIRM Training Program, Development of small molecule screens for autism using patient-derived iPS cells

**Public Summary:**
22q13.3 deletion syndrome (also known as Phelan-McDermid syndrome) is a genetic neurodevelopmental disorder characterized by global developmental delay, severely impaired speech, intellectual disability, and autism. The syndrome is caused by the heterozygous microdeletions in the terminal region of chromosome 22. Although, a candidate gene responsible for the neurological abnormalities in patients has been suggested (SHANK3, which encodes a scaffolding protein of excitatory synapses), cellular and molecular defects associated with this syndrome were unknown. In the study published in Nature today, researchers from Stanford University reported that human neurons derived from induced pluripotent stem cells of patients with Phelan-McDermid syndrome and autism have deficits in excitatory synaptic transmission due to reduced number of excitatory synapses. The authors demonstrated that SHANK3 is primarily responsible for these deficits, as neurons from patients had reduced SHANK3 expression and increasing the levels of SHANK3 expression rescued synaptic deficits in patient cells. The authors also tested several drugs for their ability to increase the number of excitatory synapses in neurons derived from patients and found that prolonged treatment with Insulin Growth Factor 1 (IGF1) completely restores excitatory synaptic transmission in patient cells. Interestingly, IGF1 produced its action by increasing the number of different type of excitatory synapses that express scaffolding protein PSD95 and lack SHANK3 expression. In summary, this study brings important insights about the cellular and molecular mechanisms involved in the loss and gain of synaptic function in human neurons from patients with Phelan-McDermid syndrome and autism. It also provides encouragement that neurons derived from induced pluripotent stem cells of patients will be useful in understanding and developing treatments for neurodevelopmental and psychiatric disorders.

**Scientific Abstract:**
Phelan-McDermid syndrome (PMDS) is a complex neurodevelopmental disorder characterized by global developmental delay, severely impaired speech, intellectual disability, and an increased risk of autism spectrum disorders (ASDs). PMDS is caused by heterozygous deletions of chromosome 22q13.3. Among the genes in the deleted region is SHANK3, which encodes a protein in the postsynaptic density (PSD). Rare mutations in SHANK3 have been associated with idiopathic ASDs, non-syndromic intellectual disability, and schizophrenia. Although SHANK3 is considered to be the most likely candidate gene for the neurological abnormalities in PMDS patients, the cellular and molecular phenotypes associated with this syndrome in human neurons are unknown. We generated induced pluripotent stem (iPS) cells from individuals with PMDS and autism and used them to produce functional neurons. We show that PMDS neurons have reduced SHANK3 expression and major defects in excitatory, but not inhibitory, synaptic transmission. Excitatory synaptic transmission in PMDS neurons can be corrected by restoring SHANK3 expression or by treating neurons with insulin-like growth factor 1 (IGF1). IGF1 treatment promotes formation of mature excitatory synapses that lack SHANK3 but contain PSD95 and N-methyl-d-aspartate (NMDA) receptors with fast deactivation kinetics. Our findings provide direct evidence for a disruption in the ratio of cellular excitation and inhibition in PMDS neurons, and point to a molecular pathway that can be recruited to restore it.